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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,292	11/23/2001	James E. Galen	UOFMD.007A	5386

23373 7590 02/10/2005

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,292	GALEN, JAMES E.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7 and 22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7 and 22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2004, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment, declaration and response filed 10-5-04 have been entered into the record. The information disclosure statement filed 1-5-05 has been entered into the record. Claims 4, 6 and 8-20 have been cancelled. Claims 1-3, 5, 7, 21-26 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Information Disclosure Statement

The information disclosure statements filed October 5, 2004 and January 5, 2005 have been considered. Initialed copies are enclosed.

Priority

Applicants argue that the claims are entitled to the date of the provisional filing. Applicant's arguments on this point are not persuasive because the claims are drawn to methods and the priority document does not perform the method of the claimed invention. Further, the provisional document does not disclose any of the sequences of the claims. Further, the provisional document only indicates that ClyA has to potential as a novel secretory protein capable of exporting passenger proteins (page 9, last paragraph). As such, the now claimed invention does not have written description support in the provisional document and further is not enabled therein. Applicants argue that pages 8-9 provide detail the construction and testing of an expression vector comprising a clyA-bla fusion. This is not persuasive it is limited to use of ClyA gene isolated from S. typhi using a particular method. Neither the sequence of the ClyA gene, nor the sequence of the S. typhi protein are disclosed. Further, the provisional document is limited to genetic fusions at the 3' terminus of the cloned ClyA gene isolated from S. typhi (page 8). The claims are not so limited. Applicants argue that the discussion of homologous proteins supports the

use of other ClyA proteins. This is not persuasive, the fusions are not enabled for reasons set forth herein and the provisional document admits ".. we have not conclusively demonstrated outright secretion of ClyA fusions out of *E. coli* and *S. typhi*.." (page 10, lines 3-4). As such, secretion of even the clyA (S. typhi) gene was not demonstrated by Applicants own admission in the priority document. Applicants argue that the provisional document provides support for the S. typhi protein and points to the provisional describing the size of the protein and the size of the open reading frame. Neither of these teaches the sequence as set forth in SEQ ID NO:2 and neither of these properties are set forth in the claims. Applicants argue page 6 of the provisional document addresses antigens. As such, the provisional document, does not comply with the provisions of 35 USC 112, first paragraph, and therefore the prior art date assigned to the instant Application is the instant filing date of 11-23-01.

Rejections Withdrawn

The rejection of claims 1-7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' amendments.

The rejection of claims 1, 3, 4, and 7 under 35 U.S.C. 102(b) as being clearly anticipated by Ikonomidis et al (J.Exp. Med. 180:2209-2218, 1994) is withdrawn in view of Applicants' amendments.

The rejection of claims 1, 3, 4, and 7 under 35 U.S.C. 102(b) as being clearly anticipated by Gentschev et al (Behring Inst Mitt, 98:103-113, 1997; of record in 1449) is maintained for reasons made of record in the Office Action Mailed 4-5-04.

Claims 1-4 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gentschev et al (Behring Inst Mitt, 98:103-113, 1997) in view of Curtis, III et al (U.S. Patent No. 5,387,744 issued February 7, 1995; of record in 1449) are maintained for reasons made of record in the Office Action Mailed 4-5-04.

Rejections Maintained

Claims 1-3, 5, 7, 21-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing a fusion protein comprising a clyA protein of Salmonella enterica serovar Typhi fused to a protein of interest in *Salmonella enterica* serovar Typhi comprising providing an expression vector to a population of untransformed *Salmonella enterica* serovar Typhi cells to produce a population of transformed *Salmonella enterica* serovar Typhi wherein the expression vector comprises an expression cassette comprising SEQ ID NO:2 operatively linked 5' to the gene encoding the protein of interest and cultivating transformed *Salmonella enterica* serovar Typhi in a bacterial medium and expressing the expression cassette to produce the fusion protein wherein the fusion polypeptide is exported from *Salmonella enterica* serovar Typhi into the bacterial medium, it does not reasonably provide enablement for methods using other clyA genes or use of any bacterial cell in combination with any clyA gene is maintained for reasons made of record in the Office Action mailed 4-5-04.

Applicant's arguments have been carefully considered but are not persuasive. Applicants reiterate the teachings of the specification that demonstration of one operative embodiment enables the family. This is not persuasive for all the reasons made of record. Applicants argue that HlyE family members are export proteins that are exported out of bacteria in which they are expressed. This argument is not persuasive because it merely reiterates that the hemolysin E is secreted in its native environment. This is not a showing that any hemolysin E is secreted from any gram negative bacterium, which includes families such as Bacteriodaceae, Vibrionaceae, Pasteurellae, Pseudomonadaceae, Neisseriaceae and Rickettsiae. That is heterologous secretion. The specification admits that the mechanism of secretion is unknown and undocumented by the specification. The interchangeability of one species of clyA with any other species of clyA protein for export purposes in heterologous gram negative bacterial cells is undocumented

by the specification and the art. Further, this is not persuasive, because it does not demonstrate successful fusion protein production and expression using any family member. It is also noted that the claims are not limited to this embodiment (homologous production). There is no evidence of record that the genus of gram-negative bacteria can support heterologous secretion of any HlyE family member. One of skill in the art would not have understood this from expression in a homologous cell using the homologous protein with a single family member. That is there is no evidence of record demonstrating interchangeability within the now claimed genus. Applicants argue with regard to claim 24, Declarant indicates that the *E. coli* HlyE protein having three of the mutations recited in claim 24, is exported from bacterial cells comprising the mutated polynucleotide. The declaration of Dr. Galen has been carefully considered but is not persuasive. The claims are drawn to "having an amino acid substitution at one or more of positions 180, 185, 187 and 193" of SEQ ID NO:2. Declarant indicates that experiments conducted by Wallace and Atkins et al demonstrate that the *E. coli* hlyE protein could be mutated in such a manner that the hemolytic activity of the protein was attenuated. The teachings of Wallace indicate that specific substitutions and replacement of V185S, A187S and I193S attenuated hemolytic activity of *E. coli* HlyE. This is not persuasive for the claims because the claims are drawn to a different hemolysin. This is also not persuasive, because, the teachings of the specification did not demonstrate secretion of the *E. coli* hemolysin fusion protein or the *E. coli* fusion protein with the hemolytic variant of the prior art. Enablement is established at the time of filing, there was no demonstration that the hemolytic variant was secreted from cells and thus at the time of filing using the information of the specification, one skilled in the art would not (a) expect or predict secretion of a fusion protein comprising the hemolytic variant of either the HlyE variant of the art or the claimed HlyE variant of SEQ ID NO:2. There is no showing in the specification that the claimed HlyE variant of SEQ ID NO:2 is secreted. Further, Appendix II of the specification demonstrates that the particular triple variant V185S,

A187S and I193S of HlyE from *E. coli* is secreted by a mutant A187G/G188R is not secreted. As such, it is clear even from the submitted evidence that success with one hemolytic mutant does not predict success with the other mutants. Further, the claims are not limited to the particular mutant and sequence. Further, there is no evidence presented as to the claimed mutants. Neither Wallace et al or Atkins et al teach the effect of individual mutations as single positions alone or in various combinations. Additionally, these documents do not place the variants in the prior art at the time the invention was made because they are published after the filing date of the provisional application. As such, they were not described before the filing of the insantly claimed invention to which Applicants argue that they are entitled. Moreover, the teachings are limited to specific substitutions with specific combinations. Declarant's own experiments indicate that different combinations of mutants unpredictably effect secretion (i.e. the double mutant of *E. coli* hlyE) is not secreted. Therefore, the evidence does not support enablement of the claimed invention at the time of filing either of the provisional or non-provisional date. There remains no evidence of record that any of the single mutations or combinations as claimed are secreted or reduced. Specific mutations of the art do not support the broad scope of mutations claimed herein. Applicants argue since the proteins are highly homologous, what works for one should work for the other. This is not persuasive, Declarant's own evidence indicates that minor differences in the *E. coli* sequence alone abolishes secretion activity of a hemolytic variant (i.e. double mutant with reduced hemolytic activity). By Declarant's own reasoning, any protein highly homologous should be likewise secreted, but this is clearly not true because the double mutant that is highly homologous, is not secreted. Therefore, the effect of changes in sequence lead to unpredictable changes in the ability to undergo secretion. The specification does not set forth secretion of any of the claimed variants, and Declarant's evidence establishes that homologous variants are not predictably secreted. Therefore, the assertion that because the claimed protein is highly homologous to the triplet mutant of *E. coli* HlyE

demonstrated to be secreted in Appendix II, the claimed protein would also be secreted is not persuasive. Finally, this is not persuasive, because Declarant's evidence is not commensurate with the claims.

For the foregoing reasons and the reasons made of record in the previous Office Action, the rejection is maintained.

Claims 1, 3 and 7 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Gentschev et al (Behring Inst Mitt, 98:103-113, 1997; of record in 1449) is maintained for reasons made of record in the Office Action Mailed 4-5-04.

Applicant's arguments have been carefully considered but are not persuasive. Applicants argue that Wallace et al teaches that Hemolysin A and hemolysin E of *E. coli* are unrelated proteins. This is not persuasive, Wallace et al is directed to a particular structure. The terms HlyE or ClyA are not defined in the specification by any particular structure and is not seen limited to any particular structure. The amendment to the claims to recite "ClyA protein (SEQ ID NO:X)" is not seen to limit to the structure because it is not clear if this is a mere example of the protein or if applicants intend to limit to the particularly disclosed sequence. Applicant's intention with this language is viewed as a mere exemplification in view of the recitation of claim 5 that indicates that the protein has the amino acid sequence of SEQ ID NO:2. This rejection is maintained until such time that the scope of ClyA is clearly and unambiguously set forth in these claims. Further, none of the particular characteristics that define ClyA/HlyE over HlyA are set forth in the claims. The recitation of a name of a gene/protein does not distinguish the gene/protein from any other similar functioning protein absent unambiguously defined structural limitations in the claims.

Claims 1-3and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gentschev et al (Behring Inst Mitt, 98:103-113, 1997) in view of Curtis, III et al (U.S.

Patent No. 5,387,744 issued February 7, 1995; of record in 1449) are maintained for reasons made of record in the Office Action Mailed 4-5-04.

Applicant's arguments have been carefully considered but are not persuasive. Applicants argue that since the rejection over Gentschev et al fails so does the combination. This is not persuasive, Gentscehv et al does not fail for the reasons set forth above. The rejection is maintained for reasons made of record.

New Rejections Based on Amendment

Specification

The amendment filed 10-05-04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows: it is noted that applicants have merely amended the sequence listing to include reference to the essential material incorporated by reference. Applicants response and amendment was not accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference at the time of filing. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). This criteria is important because as previously set forth, the sequences in GenBank are subject to changes and are not immutable in time. As such, Applicants must aver that the referenced material contains no new matter and consists of the same material incorporated by reference at the time of filing. Until such time as the declarations are filed, the specification is objected to as containing new matter. Further, the specification only specifically referenced the gene sequences and not the protein sequences. As such, the insertion of the now recited protein sequences into the sequence listing is considered new matter.

Claims 1-3, 7 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claims 1, 22, 25 and dependent claims 2, 3, 21, 23, 26 are indefinite because it is unclear if the phrase "...protein (SEQ ID NO:X)" limits the indicated protein to the particular sequence, especially in view of claim 5 that specifically recites that the export protein has the sequence of SEQ ID NO:2. Therefore, the reference to the sequence identifier in parenthesis is confusing because it is unclear if the recited proteins are limited to that sequence. As such, the metes and bounds of the independent claims is ambiguous in view of the amendatory language.

As to claim 1, while the claims can use abbreviations or acronyms such as "HlyE", the claims must first provide the entirety of the term followed by the acronym, so that there is no confusion as to the meaning of such an abbreviation/acronym. Correction is required.

Claims 1-3, 5, 7, 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As to claims 1-3, 7, 21, 25 and 26, the recitation of SEQ ID NOS:24 and 28 in the claims, rely upon the amendment of the specification to include new matter as set forth *supra*. In view of the lack of a the requisite declarations, the claims are rejected as containing new matter. Further, the specification only specifically referenced the gene sequences and not the protein sequences and therefore the insertion of the now recited protein sequences into the sequence listing is considered new matter. This issue may be resolved by amending the claims to recite "wherein the export protein is *Salmonella*

enterica serovar Typhi (S.Typhi) cytolysin A encoded by the nucleic acid sequence as set forth in SEQ ID NO:X)".

As to claims 1-3, 5, 7, 21-26, the claims now recite the subgenus of gram negative bacteria". The specification teaches "bacteria" and the specific species *Salmonella enterica* serovariant Typhi and *E. coli*. The provisional document reiterates essentially the same. Applicants believe that the provisional documents provide for support for conception of the now claimed subgenus of "gram negative bacteria" because it only teaches expression in gram negative bacteria. This is not persuasive, the provisional document does not support the now claimed subgenus because the provisional document provides contemplation of only two species *Salmonella enterica* serovariant Typhi and *E. coli*. These two species do not provide written description support for conception of the recited "gram negative" subgenus, which includes various families of gram negative bacteria unrelated to the disclosed species. The genus of gram negative bacteria include gram negative rods that are anaerobes (the family Bacteriodaceae), facultative anaerobes of the families of Enterobacteriaceae, Vibrionaceae and Pasteurealle, Gram negative cocci of the family Neisseriaceae and Gram negative obligate intracellular parasites of the family Rickettsiae. As such, the mention of two species of the family of Enterobacteriaceae does not support conception by way of written description of all gram-negative bacteria as is now claimed. The application as filed contemplates the genus of bacteria and the specific species of *Salmonella enterica* serovariant Typhi and *E. coli*, but it does not disclose the subgenus of "gram negative bacteria" as currently recited. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. In re Smith 173 USPQ 679, 683 (CCPA 1972). See MPEP 2163.05(b). Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112. The recitation of species in the provisional document does not provide basis for broadly claiming.

Claims 1, 3 and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Wallace et al (Cell, 100:265-276, Janyary 21, 2000).

Wallace et al teach the expression of a GST-HlyE (*E.coli*) fusion protein in a E. coli host cell and isolated. The *E. coli* HlyE was cloned and inserted into pGEXKG, allowing ITPG-inducible expresion of the GST-HlyE fusion protein. The fusion protein is inherently secreted, absent convincing evidence to the contrary.

Status of Claims

Claims 1-3, 5, 7 and 21-26 stand rejected.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy
Primary Examiner
Art Unit 1645